REMARKS

Reconsideration of the instant application in view of the above amendments and the following remarks is respectfully requested. Claims 42 and 44-75 are currently pending. By the present amendment, claims 42, 48, 69, and 72 have been amended and new claims 76-79 have been added, to more specifically recite certain aspects of the invention. Support for these amendments may be found throughout the specification and claims as originally filed. Therefore, the amendments do not constitute new matter. For example, support for oligonucleotides is provided on page 16, line 30; support for RNA is provided on page 13, line 19; support for double-stranded RNA is provide on page 13, lines 17-19; and support for DNA-RNA hybrids is provided on page 17, line 11. In light of these amendments, claims 47 and 71 have been canceled. It should also be noted that the above amendments are not to be construed as acquiescence with regard to the Examiner's rejections and are made without prejudice to prosecution of any subject matter removed or modified by this amendment in a related divisional, continuation or continuation-in-part application.

Rejections Under 35 U.S.C. §§ 102(e) and 103(a)

Claims 42, 44-61, and 63-75 stand rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Patent No. 5,820,873 (Choi). In addition, claims 42, 44-61, 63-64, and 67-75 stand rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Patent No. 5,885,613 (Holland). Claim 62 stands rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Choi. The Examiner points out that the instant claims are directed to compositions of matter, and asserts that both Choi and Holland teach chemical compositions identical to those disclosed by either Choi or Holland.

Applicants respectfully traverse these bases of rejection and submit that neither of the cited references anticipate or render obvious the claimed invention, since neither reference enables the making and using of the claimed nucleic acid particles and pharmaceutical compositions comprising the same.

As clearly established under U.S. patent law, a reference must teach the skilled artisan how to make and use the claimed invention, in a manner sufficient to satisfy the

enablement requirement of Section 112, in order to be anticipatory under Section 102. "In determining that quantum of prior art disclosure which is necessary to declare an applicant's invention 'not novel' or 'anticipated' within section 102, the stated test is whether a reference contains an 'enabling disclosure'... ." *In re Hoeksema,* 158 USPQ 596 (CCPA 1968). The Federal Circuit further established that the mere description of a claimed subject matter is insufficient to establish anticipation, absent teachings of how to make and use the claimed subject matter. "A disclosure in an assertedly anticipating reference must provide an enabling disclosure of the desired subject matter; mere naming or description of the subject matter is insufficient, if it cannot be produced without undue experimentation." *Elan Pharm., Inc. v. Mayo Found. For Med. Educ. & Research*, 68 USPQ2d 1373, 1376 (Fed. Cir. 2003). As stated by an earlier Court, "[P]ossession is effected if one of ordinary skill in the art could have combined the publication's description of the invention with his [or her] own knowledge to make the claimed invention." *In re Donohue*, 766 F.2d 531, 226 USPQ 619 (Fed. Cir. 1985). In contrast, when a prior art reference merely discloses the structure of the claimed compound, evidence showing that attempts to prepare that compound were unsuccessful before the date of invention will be adequate to show inoperability. *In re Wiggins,* 488 F.2d 538, 179 USPQ 421 (CCPA 1971).

Furthermore, it is clearly established that an anticipatory prior art reference must teach both "how to make" and "how to use" a claimed composition. The Federal Circuit recently addressed the issue of whether an anticipatory reference must satisfy the utility component of the enablement requirement. *Rasmussen v. SmithKline Beecham Corp.*, 75 U.S.P.Q.2d (Fed. Cir. 2005). In *Rasmussen*, the Court rejected the idea that the proposition that the enablement requirement of Section 112, first paragraph, does not mandate any showing of utility, or, if it does, it mandates only a showing that it is "not implausible" that the invention will work for its intended purpose. Instead, the Court firmly stated that mere plausibility is not the test for enablement under Section 112. Thus, an anticipatory reference must teach how to make a claimed composition in a manner fit for its intended use.

The Federal Circuit has also consistently held that a prior art reference or combination of references must provide an enabling disclosure, in order to establish obviousness.

"In order to render a claimed apparatus or method obvious, the prior art must enable one skilled in the art to make and use the apparatus or method." *Beckman Instruments, Inc. v. LKB Produkter AB*, 892 F.2d 1547, 1551 (Fed. Cir. 1989). The Court affirmed this requirement more recently, stating that, "when a *prima facie* cases of obviousness is deemed made based on similarity to a known composition or device, rebuttal may take the form of evidence that the prior art does not enable the claimed subject matter. *In re Sujeet Kumar*, 418 F.3d 1361, 1368 (Fed. Cir. 2005). The Court further remarked that an applicant may rebut an obviousness rejection based upon the fact that the method described by the prior art reference would fail produce the claimed subject matter. *Id.*

The test for both the "how to make" and "how to use" arms of the enablement requirement is whether one skilled in the art could make and use the claimed invention from the disclosure coupled with information known in the art without undue experimentation. *United States v. Techtronics, Inc.*, 8 U.S.P.Q.2d 1217 (Fed. Cir. 1988); *In re Stephens*, 188 U.S.P.Q. 659 (CCPA 1976). Specific factors which are to be considered in determining whether or not experimentation required is undue are (1) the quantity of experimentation necessary (time and expense); (2) the amount of direction or guidance presented; (3) presence or absence of working examples; (4) nature of the invention; (5) the state of the prior art; (6) the relative skills of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims. *In re Wands*, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988).

Applicants respectfully submit that the cited references cannot anticipate or render obvious the instant claims, since they do not provide an enabling disclosure of how to make or use the claimed invention. More specifically, neither reference teaches how to make or use an operative embodiment of the present invention, as required under U.S. patent law. Neither Choi nor Holland exemplify a working embodiment of the claimed invention, and neither Choi nor Holland describe a method of making an operative embodiment of the claimed invention. Accordingly, neither reference adequately teaches how to make or use the claimed invention, and neither reference can anticipate or render obvious the instant claims.

Applicants respectfully submit that the present invention provides novel nucleic acid-lipid particles, which could not be effectively made or used in light of the teachings of

either Choi or Holland. Rather, it is only the teachings of the instant application, which describe a novel method of encapsulating nucleic acid particles, that enable the making and using of the presently claimed nucleic acid-lipid particles.

While Choi and Holland generally recite nucleic acids in a laundry list of potential active agents that might be considered for encapsulation in their particular liposome species, these references provide no specific or enabling teachings in this regard. The teachings of Choi are directed to liposomes having increased circulation longevity and reduced aggregation, which comprise a PEG-modified lipid, focusing on the composition and concentration of the PEG-modified lipid. Holland describes fusogenic liposomes, which comprise a bilayer stabilizing component, in addition to any of a wide range of other lipids capable of adopting a non-lamellar phase or a bilayer structure in the presence of the bilayer stabilizing component. Holland focuses almost exclusively on the composition and concentration of the bilayer stabilizing component. The mere description of nucleic acid active agents is insufficient to establish enablement with regard to the claimed nucleic acid-lipid particles, as clearly held under *Elan Pharm., Inc.*

Furthermore, the methods described in the prior art references result in an inoperative nucleic acid-lipid composition and, thus, are not enabling for the presently claimed invention. As described in the Declaration of Dr. Ian Maclachlan submitted on April 4, 2005, the method described in both Choi and Holland is inoperative with regard to both the making and using of the claimed nucleic acid-lipid particles. This method is extraordinarily inefficient in the encapsulation of nucleic acid, and the vast majority of nucleic acid is lost during the process (Paragraph 19 and Exhibit D).

While approximately 7-15% of final yield plasmid was found to be encapsulated in lipid formulations prepared according to the methods of Choi and Holland, it is important to note that 98.0-98.5% of the plasmid DNA initially formulated with the liposomes was lost during the extrusion process. Thus, only 0.1-0.3% of the plasmid DNA initially added to the formulation is encapsulated in the extruded liposomes. In support of this finding, an additional unexecuted Declaration of Dr. Ian Maclachlan is provided with this Amendment. An executed copy of this Declaration will be provided shortly. This Declaration provides further analysis of

the results of Dr. Maclachlan's attempts to use the method described in Choi and Holland to produce the claimed nucleic acid-lipid particles. As described in Paragraph 9 and shown in Exhibit B, only 0.21% or 0.14% of the input nuclei acid was recovered and encapsulated post-extrusion. It is unquestionable that such a drastic loss of input plasmid indicates that Choi and Holland are essentially inoperative, and thus non-enabling, with regard to the production of the claimed nucleic acid-lipid particles.

In conclusion, the teachings of Choi and Holland are not enabling for the production of the claimed nucleic acid particles, since they fail to teach how to make or use the claimed nucleic acid-lipid particles. The methods described in Choi and Holland are essentially inoperative, particularly given the incredible loss of nucleic acid during extrusion, and the resulting particles are inoperative for their intended use, particularly given the small amount of encapsulated nucleic acid. Given the lack of knowledge in the art at the time of the cited references with regard to methods of encapsulating nucleic acids, it would clearly require undue experimentation to make or use the claimed nucleic acid-lipid particles, in light of the inoperative teachings provided by Choi and Holland. Since Choi and Holland are not enabling for the claimed invention, they cannot be valid prior art references under Sections 102 or 103. Accordingly, Applicants respectfully request that these bases of rejection be reconsidered and withdrawn.

Rejection Under 35 U.S.C. § 112, First Paragraph, Written Description

Claims 42 and 44-75 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. More specifically, the Examiner asserts that the specification and claims do not adequately describe the structural attributes of the claimed nucleic acid-lipid particles that inhibit particle aggregation and render a nucleic acid encapsulated and resistant from degradation.

Applicants respectfully traverse this rejection and submit that the instant application provides adequate written description of the presently claimed invention, including the features that inhibit particle aggregation and render a nucleic acid encapsulated and resistant from degradation. Applicants respectfully submit that the claims clearly recite the structural

components of the claimed nucleic acid-lipid particles, and the specification provides further description of each of these components. For example, cationic lipids are described on page 15, lines 14-26; non-cationic lipids are described on page 15, line 27-page 16, line 26; nucleic acids are described on page 13, lines 17-22; and conjugated lipids are described on page 16, lines 14-17. Clearly, this description demonstrates that Applicants had possession of the claimed invention at the time of filing the instant application.

Applicants further submit that the skilled artisan would appreciate from the teachings of the instant specification that each of the specific lipid or nucleic acid components can vary significantly, while retaining the recited functional properties, since it is the general nature and combination of components that achieves the desired result, as opposed to any one specific species of component. For example, it is understood that cationic lipids are used to neutralize a portion of the negative charge associated with nucleic acid molecules, as described on page 29, lines 8-10. Also, it would be readily understood by one of skill in the art that any of a variety of conjugated lipids would serve to inhibit aggregation, and that any of a variety of different nucleic acid molecules cold be used according to the invention, as described throughout the instant application.

Further, applicants note that under the Examination Guidelines set forth by the Patent and Trademark Office, the written description requirement for a claimed genus may be satisfied by the description of a representative number of species or the disclosure of relevant, identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. Guidelines for Examination of Patent Applications under 35 U.S.C. § 112, ¶1, "Written Description" Requirement, 66 Fed. Reg. 1099, at 1106. Applicants submit that the instant application both describes a representative number of claimed nucleic acid-lipid particles, and also describes relevant, identifying characteristics of the claimed particles sufficient to meet the written description requirement.

Applicants submit that the instant specification describes a representative number of claimed species, since it describes at least five different species of claimed particles, each comprising a different cationic lipid, and all of which provide increased encapsulation of nucleic acids, as shown in Figure 41. Applicants submit that these five species provide adequate written

description support for the claimed genus. In addition, and as noted above, Applicants submit that the skilled artisan would immediately recognize that the claimed invention could comprise any of a large variety of cationic lipids, non-cationic lipids, conjugated lipids, and nucleic acids. This is further supported by the results of Example 13, which indicate that three different monovalent cationic lipids behave in similar fashion in the nucleic acid-lipid particles of the present invention.

In addition, Applicants submit that the instant specification discloses sufficient identifying characteristics to support the claimed particles, since it provides in-depth description of both structural and functional characteristics of the claimed particles. As described in the claims and throughout the instant specification, the claimed nucleic acid-lipid particles comprise a cationic lipid, a non-cationic lipid, a conjugated lipid, and a nucleic acid, wherein said nucleic acid is encapsulated in the lipid of said particle and is resistant in aqueous solution to degradation with a nuclease. These recited features serve to sufficiently identify the claimed nucleic acid-lipid particles, and thereby further demonstrate that Applicants had possession of the claimed invention at the time of filing the instant application.

In light of the above amendments and these remarks, Applicants submit that the instant application satisfies the written description requirement and respectfully request that this rejection be withdrawn.

The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

Applicants respectfully submit that all of the claims remaining in the application are allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

Respectfully submitted,

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